

REMARKS

The claims

In accordance with the suggestion of the Examiner in an interview held with applicant's representatives on May 25, 2000, the claims which recited "effective to treat cancer" have been amended to recite "effective to reduce the number of tumor cells in the patient compared to the number of tumor cells if the patient is not so treated." This phraseology is clearly inherent in the term "treating." Furthermore, also in accordance with the suggestion of the Examiner, the claims have been amended to recite methods by which the extracts can be prepared, *e.g.*, "are preparable by a) homogenizing cells in the presence of NP40, or b) treating a cell with an acid, or c) treating a cell with a proteolytic enzyme." Support for c) is found, *e.g.*, in the specification at page 3, lines 7-9.

For clarity, the claims 10-24 have been rewritten as claims 25-39: Claims 25-29 correspond to claims 17-21; claims 30-34 to claims 10-14; and claims 35, 36, 37, 38 and 39 to claims 24, 16, 15, 23 and 22, respectively.

The rejections under 35 USC 112

With regard to the rejections under 35 USC 112, second paragraph, the claims clearly recite that the amount of MHC molecules in *each* of the two containers is effective for the recited treatment. See, *e.g.*, claim 25, which recites that *each* of the containers comprises an amount of MHC molecules which is effective to reduce the number of tumor cells in a patient compared to the number of tumor cells if the patient is not so treated. Also, as was clarified in the Reply of July 8, 1999, in the third paragraph of the Remarks section, the two sources of animal tissue, serum or cells of, *e.g.*, claim 25, encompass any combination of MHC

molecules taken from different species (or from different members of the same species, *e.g.*, in the case of certain alloantigens) or from different tissues, sera or cells of the same animal.

With regard to the rejections under 35 USC 112, first paragraph, and the further clarification of the issues in the interview held on May 25, 2000, there appear to be three outstanding issues: 1) whether the specification is enabling for cross-tissue operability, *e.g.*, the use of MHC molecules from one type of tissue to treat cancers originating from another type of tissue; 2) whether the specification is enabling for cross-species operability, *e.g.*, the use of MHC molecules from one species to treat cancers in another species; and 3) whether the claimed MHC preparation contains, as its active principal, MHC molecules or associated molecules. Other issues, such as the relevance of the disclosed animal model, were addressed in the Reply of July 8, 1999 and, based on the discussion during the interview, have apparently been resolved.

1) cross-tissue operability - The Examiner has not formally presented evidence or sound scientific reasoning to cast doubt on applicant's assertion that the claimed method is operable in a cross-species fashion. Nevertheless, applicant submits the attached Declaration (sections 4-8), which clearly shows that MHC preparations from liver exhibit an *in vivo* effect on tumor cells derived from at least two other tissues, *i.e.*, such MHC preparations inhibit the growth of mesothelioma cells, and impair tumor recurrence of colon tumor cells. Furthermore, the specification teaches that MHC from a variety of tissues, sera or cell sources, including red blood cells, can be used to treat cancers which originate from other tissue sources (see, *e.g.*, specification at page 4, lines 9-13).

2) cross-species operability - The Examiner has not formally presented evidence or sound scientific reasoning to cast doubt on applicant's assertion that the claimed method is operable in a cross-species fashion. Nevertheless, applicant submits the attached Declaration,

which shows that MHC preparations from calf inhibit the growth of tumor cells in two other species of animal: mouse and rat (sections 4-8), and that an MHC preparation from calf inhibits the growth of human cells (HT29 human colon carcinoma cells, inoculated into a nude rat) (sections 4 and 9). Furthermore, the specification teaches that MHC molecules from a variety of species, *e.g.*, bovine red blood cells, or liver from pig, calf or goat, can be used to treat cancers which originate from heterologous species (see, *e.g.*, specification at page 3, "Summary of the Invention" and original claim 7). In particular, MHC from calf (*e.g.*, Example A, pages 7-8) or goat (*e.g.*, Example B, page 8), or combinations thereof, is shown to inhibit tumors derived from, *e.g.*, rat tissue (Yoshida AH-130 cells).

3) The active principal in the MHC preparations is, in fact, MHC

The attached Declaration¹ (see section 4, paragraphs 5 and 7) describes at least two types of preparations of extracts: fractions which test positive against, *e.g.*, an MHC-specific monoclonal antibody [MoAb H42A (MHC class II D.B.A. Italia, Segrate)], and fractions which test negative against such monoclonal antibodies, *e.g.*, against MoAb H42A and H58A (MHC class I D.B.A. Italia, Segrate). The latter, control fractions, are referred to in the Declaration as "T-14." The Declaration shows that, in a variety of assays, the former preparations exhibit activity against tumor cells, whereas the control T-14 fractions do not. See, *e.g.*, sections 5-8. These observations support the conclusion that the active principal in the MHC preparations of the invention is, in fact, MHC.

Furthermore, as discussed in the Reply of July 8, 2000 (page 4, section 2), the MHC preparations of the invention do not contain components other than MHC which exhibit therapeutic effects. The detergent extraction methods disclosed, *e.g.*, in Example II, are well-

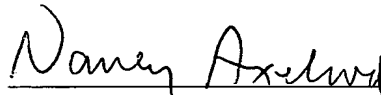
¹The attached Declaration has not been signed by the inventor. An executed copy will be filed shortly.

known in the art to selectively extract MHC molecules. See, e.g., specification, p. 3, second paragraph; and Labeta *et al* (1988). *Journal of Immunological Methods* 112, 133-138, cited in the search report of the PCT and of record herein. Such an extract is demonstrated to be effective. See, e.g., Figure 5.

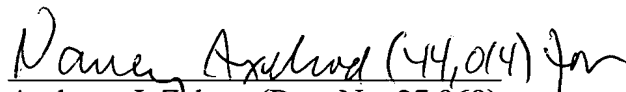
Furthermore, the attached Declaration (section 11) shows that a synthetic peptide from an MHC molecule exhibits antitumor activity which is similar to that of an MHC preparation of the invention. This supports the conclusion that the active ingredient in the MHC preparation is, in fact, one or more MHC or associated molecules.

In view of the preceding amendments and remarks, the application is believed to be in condition for allowance, which action is respectfully requested. However, if the Examiner has questions or would like to discuss any of the issues further, she is invited to telephone the undersigned.

Respectfully submitted,



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